REMARKS/ARGUMENTS

I. Status of the claims

Claims 1, 2, 6, 7, 11, 16, 17, 21, 26, 31, 32, 33, 35, 39, 40, 41, 45, 46, 50, and 51 are amended and claims 82-99 are added. Claims 4-5, 8-10, 14-15, 18-20, 24-25, 27-30, 36-38, 42-44, 47-49, and 52-81 are canceled. Claims 1-3, 6-7, 11-13, 16-17, 21-23, 26, 31-35, 39-41, 45-46, 50-51, and 82-99 are pending with entry of this amendment.

Applicants thank the examiner for her assistance in generating an office action in a timely fashion.

II. Support for the amendments

Support for the amendments to the claims can be found in the specification and originally-filed claims. For example, support for introduction of R or Q into position 4 of SEQ ID NO:1 can be found, e.g., page 11, lines 23-26 of the specification. No new matter is added.

III. New matter rejection

The Examiner rejected a number of claims for allegedly containing new matter. Specifically, the examiner argued that the recited consensus sequence (SEQ ID NO:1) did not reflect sequences in the non-*Thermus* species recited in the claims. As amended, the bacterial species are not recited in the independent claims. Therefore, Applicants respectfully request withdrawal of the rejection.

IV. Obviousness rejections

A. Rejections over Brandis in view of Abramson

The Examiner rejected a number of pending claims as allegedly obvious over Brandis I in view of Abramson. The Examiner also rejected the same pending claims as allegedly obvious over Brandis II or III in view of Abramson. Because the Brandis references all appear to have an identical disclosure, the following discussion does not generally distinguish between the different Brandis references, and is intended to apply to each Brandis reference

equally. According to the Examiner, Brandis describes making specific *Taq* mutants (including E681K) that have lower discrimination for fluorescein-labeled nucleotides. While Brandis did not refer to some of the recited *Thermus* species, the Examiner argues it was obvious to introduce the E681K mutation into other *Thermus* polymerases, such as polymerases described by Abramson.

Applicants respectfully traverse the rejection. In order to expedite prosecution, Applicants have amended the claims such that they are directed to polymerases in which position 4, as defined in the claims, is Arg (R) or Gln (Q).

The Brandis reference does not teach or suggest what effect, if any, mutation of position 4 to R or Q would have on incorporation of fluorescein-labeled nucleotides. Brandis I states the following at col. 8, ll. 9-15:

> Preferred positions for substitution mutations are R595, D655, R660, and E681. A particularly preferred position for mutations is E681, with the preferred substitution at position 681 being M. Other suitable substitution mutations at E681 are as follows (listed in order of decreasing preference, excpt where note by a equal sign to denote approximate equivalence"): M>I>W>L>V>P>H=K=G=T=S>D=A=N>Y=C.

The above-quoted text does not teach or suggest that amino acids other than those listed can be substituted at position 681.

In fact, the Brandis reference teaches away from the claimed invention. Prior art references that "teach away cannot serve to create a prima facie case of obviousness." *See McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1354 (Fed.Cir. 2001). The recent *KSR* Supreme Court case also acknowledged that art that "teaches away" from an invention is important in an analysis of non-obviousness. *See, e.g., KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1395 (2007) and the Court's discussion of the *United States v. Adams*, 383 U. S. 39, 40 (1966) decision: "The Court relied upon the corollary principle that when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious"

The Brandis reference, and the above-quoted text from column 8 in particular, teaches away from insertion of either Q or R because the Brandis reference omits Q and R but implies that the listing of possible substitutions is complete. For example, by stating that "[o]ther sutable mutations at E681 are as follows", Brandis suggests that the listed substitutions are the only substitutions possible (implying others are unsuitable). Indeed, the ranking of the substitutions by Brandis further implies that the first-listed substitution ("M") is the best possible mutation to reduce discrimination and that the last listed substitution ("C") is the substitution that reduces discrimination the least while achieving at least some discrimination. Thus the ranking implies to the reader that the possible universe of functional substitutions is what is listed in Brandis. Such disclosure thus teaches away from other substitutions that are not expressly described in the Brandis reference.

As described in the Declaration of Dr. David Gelfand (originally filed January 3, 2003), both Q and R substitutions (as recited in the amended claims) generate improved discrimination over the wildtype *Thermus* "E". Notably, substitution with R in particular resulted in the best discrimination of all 19 possible amino acids. These results thus represent superior results that could not have been predicted from the cited art. The superior results of the R substitution in particular is surprising in view of Brandis's teaching that substitution with M is best. While M provides for lower discrimination than many possible substitutions, Dr. Gelfand's declaration demonstrates that in fact that several substitutions (including R) are surprisingly superior.

It should be noted that the new Patent Office obviousness guidelines are limited by the law set forth in both the *KSR* Supreme Court decision (discussed above) and the recent *Pfizer, Inc. v. Apotex, Inc.*, 82 USPQ2d 1321 (Fed. Cir. 2007) decision. Notably, the *Apotex* case only found the invention in question obvious after finding two things: (1) that a base and acid would chemically react, **and** (2) that the salt in question "would work for its intended purpose." *See, Pfizer v. Apotex,* at 1335 (stating "Simply put, to conclude that amlodipine besylate would have been obvious, 'the prior art, common knowledge, or the nature of the problem, viewed through the eyes of an ordinary artisan' merely had to suggest reacting amlodipine base with

benzene sulphonic acid to form the besylate acid addition salt, and that that acid addition salt form would work for its intended purpose. *DyStar*, 464 F.3d at 1361. They did."). Under the facts of the claims currently under examination, there is no clear teaching what the "intended purpose" of the amino acid substitutions was or would be, in contrast to the established pharmaceutically-acceptable salts at issue in the *Pfizer* case.

> This same issue is also emphasized when the Court stated the following:
>
> However, on the particularized facts of this case, consideration of the "routine testing" performed by Pfizer is appropriate because the prior art provided **not only** the means of creating acid addition salts **but also predicted the results**, which Pfizer merely had to verify through routine testing.
> *See Pfizer v. Apotex*, 82 USPQ2d 1321, 1335 (emphasis added)

Again, for the currently claimed subject matter, it is difficult to understand how the cited art could have "predicted the results" of substituting R or Q when the art did not even discuss such substitutions or their effects.

In summary, the amended claims are not obvious from the art because the art did not teach, and in fact taught away from the possibility of substituting Q or R into position 4 of SEQ ID NO:1. Further, as shown in the Declaration of David Gelfand, substitution with R reduces the levels of discrimination more than any other substitution. Such results were not predictable from the cited art and are surprisingly superior results. Accordingly, withdrawal of the rejections is respectfully requested.

B. Rejection over Brandis, Abramson, and

The Examiner rejected claims 32, 50-52, 67-68, and 79-80 as allegedly obvious over Brandis I, II, or III, each in view of Abramson and Gelfand. According to the Examiner, Brandis and Abramson teach or suggest introduction of the E681K mutation into other *Thermus* polymerases, but do not teach combination of the E681K mutation with a mutation at *Taq* position 615. However, the Examiner argues that Gelfand describes advantages of the 615

mutation and therefore it is allegedly obvious to combine the 681 and 615 mutations in a polymerase.

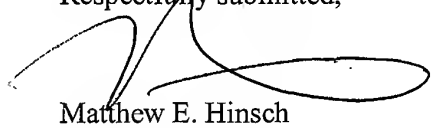
Applicants respectfully traverse the rejection. As explained above, the Brandis and Abramson references, when combined, do not teach or suggest the subject matter of the amended claims. As the Examiner's rejection was directed to different claimed subject matter than currently pending, Applicants respectfully submit that the rejection is moot. Withdrawal of the rejection is therefore respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,



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